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Catalytic asymmetric chiral lithium amide-promoted epoxide rearrangement: a NMR spectroscopic and kinetic investigation

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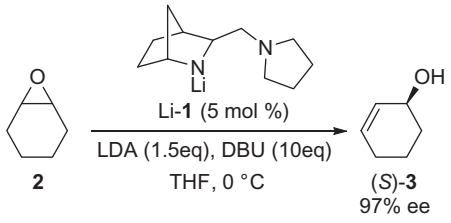
ABSTRACT

The lithium amide derived from the chiral diamine (1*R*,3*S*,4*S*)-3-(1-pyrrolidinyl)methyl-2-azabicyclo[2.2.1]heptane, has been reported to catalytically deprotonate cyclohexene oxide and other epoxides, yielding chiral allylic alcohols in excellent enantiomeric excess. In this work, ^{6}Li, ^{1}H and ^{13}C NMR spectroscopy have been used to study the aggregation of the chiral lithium amide in THF and the influence on the aggregation by the addition of additives, such as 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU). The activated complex under catalytic deprotonation of cyclohexene oxide, that is, with excess Li-DBU and free DBU, is built from one monomer of the chiral lithium amide, one molecule of epoxide and one additional molecule of DBU. The reaction order (−0.97) obtained for the bulk base Li-DBU shows an inverse dependence on the concentration, suggesting a deaggregation of the initial mixed dimer to a monomer-based transition state containing a monomer of the lithium amide.

1. Introduction

Stereoselective deprotonations by chiral lithium amides of epoxides, ketones, and so on, have found increasing use in synthetic chemistry, for example, to make biologically interesting compounds.[1] Since the report by Whitesell and Fellman[2] on the first asymmetric deprotonation of cyclohexene oxide yielding 2-cyclohexen-1-ol, significant progress has been made, a large number of structurally diverse chiral lithium amides have been synthesized and their stereoselective capabilities evaluated.[3–13] In the deprotonation reaction, the chiral lithium amide is consumed and the corresponding chiral amine is formed.[14–17] Therefore, it is desirable to be able to regenerate the chiral base during the reaction, and thereby use catalytic amounts of the chiral lithium amide. Lithium diisopropylamide (LDA) has been used as a bulk base to regenerate the chiral lithium amide from the chiral amine. However, this procedure resulted in lower stereoselectivities compared to deprotonation under stoichiometric conditions. It has been assumed that this is due to competing (racemic) reaction by LDA. However, improvements in both stereoselectivity and reactivity have been achieved by the addition of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) to the catalytic mixtures as first reported by Asami.[18]

Andersson et al. reported excellent stereoselectivity and reactivity in the deprotonation of epoxides with the chiral lithium amide Li-**1** derived from diamine (1*R*,3*S*,4*S*)-3-(1-pyrrolidinyl)methyl-2-azabicyclo-[2.2.1]-heptane **1** in the presence of LDA as the bulk base and DBU as an additive (Scheme 1).[7,10,19,20] In order to explain the change in the reactivity and enantioselectivity, DBU was suggested to solvate the lithium amide and hence decompose lithium amide aggregates into smaller aggregates.[19–21]



Scheme 1. Catalytic enantioselective deprotonation of cyclohexene oxide.

Ahlberg et al. showed that LDA also deprotonates DBU yielding lithiated DBU (Li-DBU) under these conditions. An equilibrium is set up between LDA and DBU on one side and Li-DBU and diisopropylamine (DIPA) on the other.[15] It was found that Li-DBU together with the chiral lithium amide Li-**5** forms a new complex, namely a mixed dimer Li-**5**·Li-DBU (Scheme 2).

Herein we report a detailed NMR spectroscopic investigation of the initial states and a kinetic study of the reaction orders of the system. The study shows the nature of the reagents and the composition of the rate limiting activated complexes, which show the intricate role of DBU and Li-DBU. The results are interpreted in the light of findings with some previously used bulk bases.

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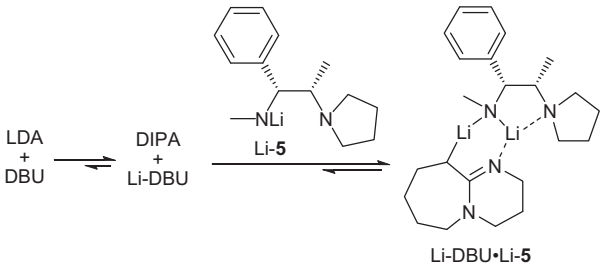
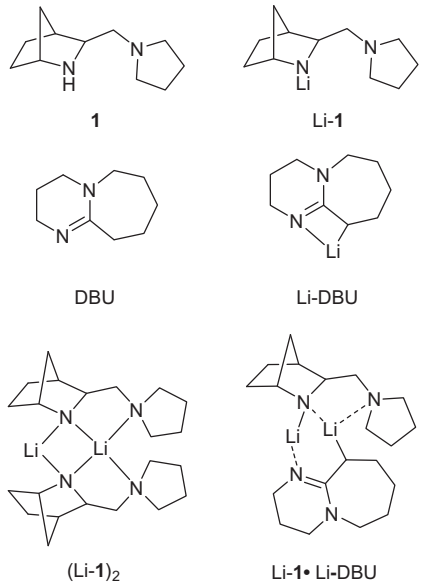


Scheme 2. LDA deprotonates DBU and forms mixed dimers with the chiral lithium amide **5**.

2. Results and discussion

2.1. NMR-spectroscopic study

Organolithium chemistry is a complex chemistry since lithium organic compounds aggregate in solution and interconvert between different types of aggregates. Therefore, studies of these aggregates of lithium amides in solution, and how solvents and additives influence these aggregates, become essential. The composition of the reagents in a solution of Li-**1** in deuterated THF at −90 °C has been investigated using ^{6}Li, ^{1}H and ^{13}C NMR spectroscopy (Scheme 3). The ^{6}Li-labelling of reagents was carried out using *n*-Bu-[^{6}Li] as the lithiating agent.



Scheme 3. Structures of precursors and their lithiated counterparts and dimeric complexes.

2.1.1. Deprotonation of 1 by *n*-BuLi

The addition of diamine **1** (1 equiv, 0.2 mmol) to a solution of *n*-Bu[^{6}Li] (0.2 mmol, 0.3 M) in THF-d_8 at −90 °C in a NMR tube (see Section 4) gave a clear solution. The ^{6}Li NMR spectrum showed two major signals (∂ 1.54, ∂ 0.78) in a 1:1 ratio and also two minor signals (∂ 1.72 and ∂ 1.44) with about equal intensity (Fig. 1a). The ratio between the pairs of signals was 6:1. The pair of signals with the higher intensity is suggested to come from a dimer (Li-**1**)$_2$ with two non-equivalent lithiums. This result is in line with previous reports that lithium amides exist as dimers with equivalent or non-equivalent lithiums.[9,22] Additives such as DBU have been used to

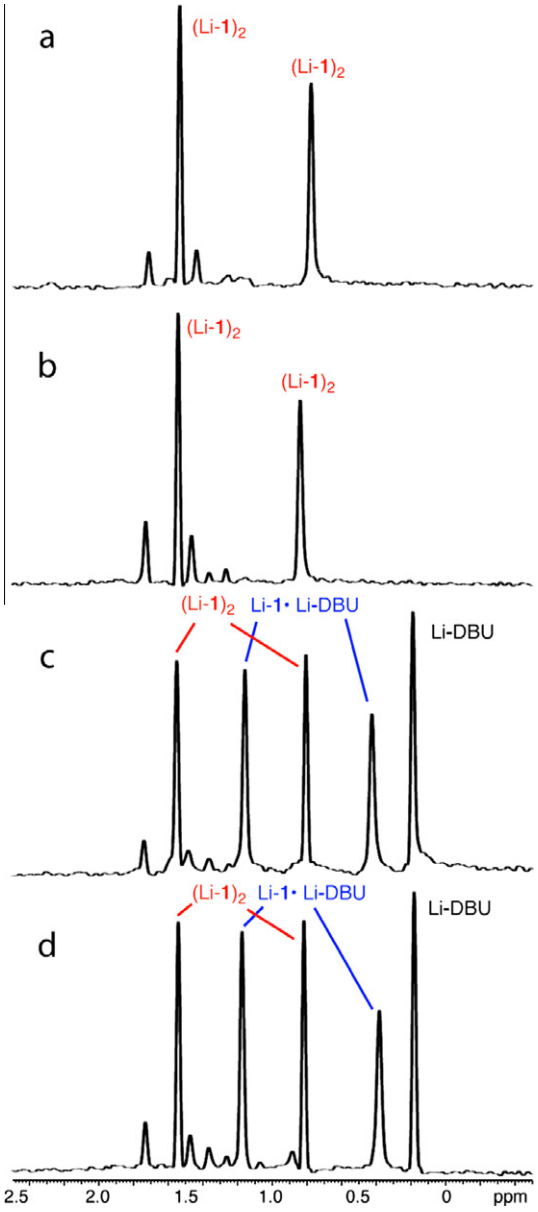
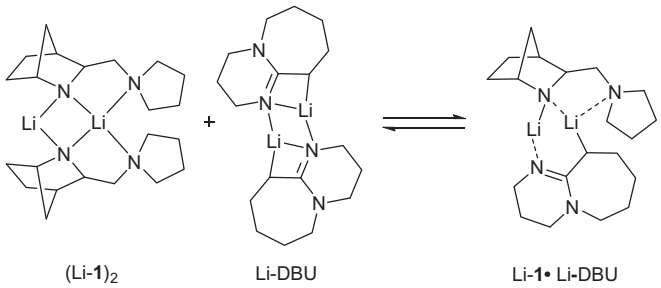


Figure 1. ^{6}Li NMR spectra obtained at −90 °C of a THF-d_8 solution of 0.3 M Li-**1** and added DBU and Bu[^{6}Li]: (a) 0.3 M *n*-Bu[^{6}Li] and 1.0 equiv **1**; (b) 1.0 equiv DBU; (c) 1.0 equiv *n*-Bu[^{6}Li]; (d) 1.0 equiv DBU.

improve the reactivity and enantioselectivity of lithium amides. It has been assumed that additives, such as DBU, deaggregate the lithium amides, and hence increase the reactivity of the lithium amide. In order to investigate the possible solvation effects on (Li-**1**)$_2$, DBU (1 equiv, 0.2 mmol) was added to a solution of (Li-**1**)$_2$. The addition caused only minor changes in the chemical shifts of the signals (Fig. 1b). However, the intensity of the minor signals (∂ 1.73, ∂ 1.47) had increased slightly relative to the major singlet (∂ 1.54, ∂ 0.84), which is probably due to the DBU solvation. However, the ^{6}Li spectrum showed no new signals originating from aggregates other than (Li-**1**)$_2$. Furthermore, the ^{6}Li or ^{13}C NMR spectra showed no evidence of the presence of lithiated DBU, which shows that Li-**1** is not a strong enough base to deprotonate DBU. The addition of a second equivalent of *n*-Bu[^{6}Li] (1 equiv, 0.2 mmol) to the DBU containing mixture gave rise to three new signals in the ^{6}Li spectrum at ∂ 0.18, ∂ 0.42 and ∂ 1.15 (the latter two of equal intensity) in addition to the signals from (Li-**1**)$_2$. Comparison with earlier results obtained by Ahlberg et al. indicates that

the signal at ∂ 0.18 corresponds to lithiated DBU (Li-DBU).[15] This is further supported by the appearance of one signal at ∂ 164.4 in the ^{13}C NMR spectrum. Previously, it has been shown that the carbon at the 7-position in DBU shifts from ∂ 160.1 to ∂ 164.4 upon deprotonation to yield Li-DBU. The other two new signals (∂ 0.42 and ∂ 1.15) are suggested to come from a novel complex—a mixed dimer (Li-**1**·Li-DBU)—built from a monomer of Li-**1** and a monomer of Li-DBU (Scheme 4).



Scheme 4. (Li-**1**)$_2$ and (Li-DBU)$_2$ is in equilibrium with the mixed dimer Li-**1**·Li-DBU.

The two lithiums in these mixed dimers are non-equivalent. This is in analogy with the mixed dimer that has been shown to form between the Li-**5** and Li-DBU (Scheme 2). This conclusion is further supported by the ^{13}C NMR data. A closer inspection of the ^{13}C NMR spectrum of the mixture reveals that there is also a signal slightly downfield (∂ 164.9) of the signal belonging to lithiated DBU (∂ 164.4). It has previously been found that the amidine carbon upon mixed dimer formation is shifted slightly downfield (∂ 165.4).[15]

It is noteworthy that the ^{6}Li NMR spectrum (Fig. 1c) shows that not all Li-DBU (presumably present as a dimer) and (Li-**1**)$_2$ have reacted with each other to yield the mixed dimer Li-**1**·Li-DBU. Instead an equilibrium has been established in which there is about equimolar amounts of (Li-**1**)$_2$ and Li-**1**·Li-DBU and about half as much of (Li-DBU)$_2$ in the solution. Further addition of DBU (1 equiv, 0.2 mmol) gave only minor changes of the ^{6}Li NMR chemical shifts of the signals. Further addition of DBU (3 equiv, 0.6 mmol; in total 4 equiv) resulted in formation of needle-like crystals in the brownish solution. A X-ray crystallographic study revealed that these were composed of Li-DBU dimers [(Li-DBU)$_2$] with each of the 2 equiv lithium coordinated to a DBU molecule (Fig. 2, unpublished data).

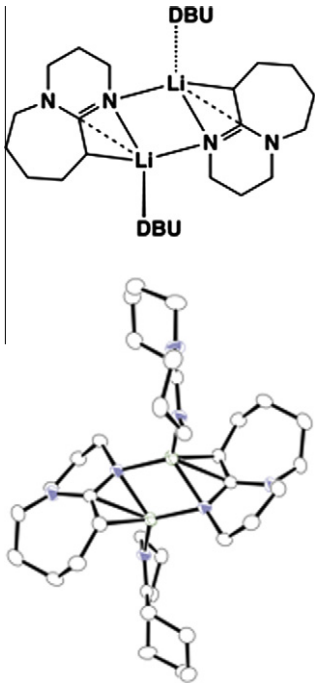


Figure 2. X-ray structure of crystals formed in the NMR-tube at −90 °C in THF (unpublished data).

2.1.2. Deprotonation of 1 using Li-DBU

The ^{6}Li-NMR spectrum at −90 °C of a solution of Li-DBU (0.3 M, 0.2 mmol) in THF displays only a singlet as previously reported (Fig. 3a).[15] The addition of diamine **1** (0.5 equiv, 0.1 mmol) gave a yellow clear solution with the spectrum shown in Figure 3b. The chemical shifts and relative intensities were similar to those in the spectrum in Figure 1c of a solution containing (Li-DBU)$_2$, (Li-**1**)$_2$ and mixed dimer Li-**1**·Li-DBU. It appears that (Li-DBU)$_2$ is a strong enough base to deprotonate the chiral diamine. The further addition of chiral diamine (0.5 equiv, 0.1 mmol) gave the spectrum shown in Figure 3c, which is closely similar to the one displayed in Figure 1b. This shows that all of the added Li-DBU had been consumed in the deprotonation of the diamine. The spectrum in Figure 3d shows that Li-DBU is regenerated by the addition of *n*-Bu[^{6}Li] (1 equiv, 0.2 mmol) yielding an equilibrium mixture of the dimers (Li-**1**)$_2$ and (Li-DBU)$_2$, and the mixed dimer Li-**1**·Li-DBU with about the same composition as that of the solution in Figure 1c. The formation of mixed dimer Li-**1**·Li-DBU was confirmed by the ^{13}C NMR spectrum showing two signals at ∂ 164.4 and ∂ 164.6, corresponding to Li-DBU and Li-**1**·Li-DBU, respectively. The addition of DBU (1 equiv, 0.2 mmol) to this mixture only caused minor changes as shown by the spectra in Figure 3e (or Fig. 1d). The addition of another equivalent of *n*-Bu[^{6}Li] (1 equiv, 0.2 mmol) generated another equivalent of Li-DBU and this (Fig. 3f) changes the composition of the equilibrium favoring the mixed dimer Li-**1**·Li-DBU over the dimer with two non-equivalent lithium (Li-**1**)$_2$.

Increasing the concentration of Li-DBU shifts the equilibrium towards the mixed dimer. Under the catalytic conditions, the lithiated DBU concentration is 40 times higher than the concentration of Li-**1**, which means that the equilibrium is completely shifted towards the mixed dimer. With these experimental results as a basis, we turned our attention to an investigation of the reagent composition when using LDA as a deprotonating agent rather than of *n*-Bu[^{6}Li].

2.1.3. Deprotonation of 1 using LDA

The addition of *n*-Bu[^{6}Li] (1 equiv, 0.2 mmol) to diisopropylamine (0.3 M, 0.2 mmol) in THF-d_8, gave a clear solution. The ^{6}Li NMR spectrum at −90 °C (Fig. 4a) showed one major singlet (∂ 1.91) originating from LDA (a dimer in THF[23]).

The addition of chiral diamine **1** (0.5 equiv, 0.1 mmol) to the LDA-solution, gave the ^{6}Li-spectrum shown in Figure 4b. It shows three major peaks, one originating from LDA (∂ 1.92) and two new signals of equal intensity at ∂ 1.54 and ∂ 0.77 corresponding to (Li-**1**)$_2$. Obviously, LDA is a strong enough base to deprotonate the diamine **1**. The spectrum gives no indication of the formation of any mixed dimer between LDA and Li-**1**.

The further addition of diamine (0.5 equiv, 0.1 mmol) was found to consume the remaining LDA as indicated by Figure 4c. The LDA signal disappeared and the remaining signals originate from the lithiated diamine (Li-**1**)$_2$. This shows that LDA is capable of fully deprotonating **1** and (Li-**1**)$_2$ is strongly favored in the equilibrium. After the addition of another equivalent of *n*-Bu[^{6}Li] (1 equiv, 0.2 mmol), LDA was regenerated as shown by the reappearance of the singlet at ∂ 1.92 in the ^{6}Li spectrum (Fig. 4d). Addition of DBU (1 equiv, 0.2 mmol) to this solution gave the spectrum

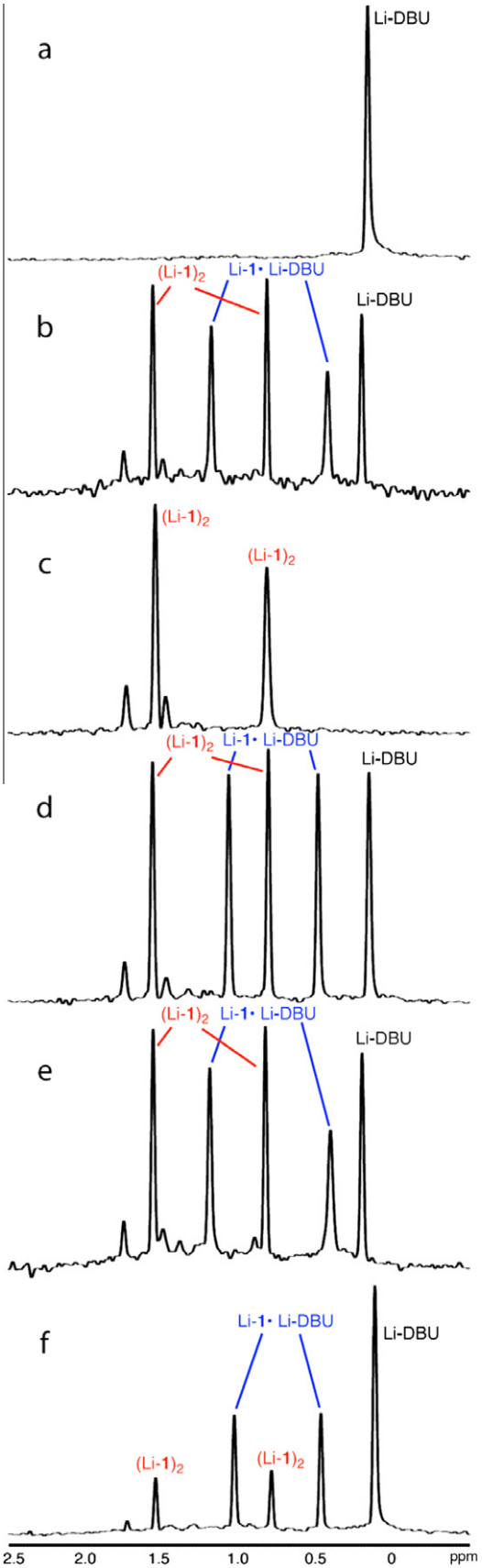


Figure 3. ^{6}Li NMR spectra obtained at −90 °C of a THF-d_8 solution of 0.3 M Li-DBU and added **1** and *n*-Bu[^{6}Li]: (a) 0.3 M Li-DBU; (b) 0.5 equiv **1**; (c) 1.0 equiv **1**; (d) 1.0 equiv *n*-Bu[^{6}Li]; (e) 1.0 equiv DBU; (f) 1.0 equiv *n*-Bu[^{6}Li].

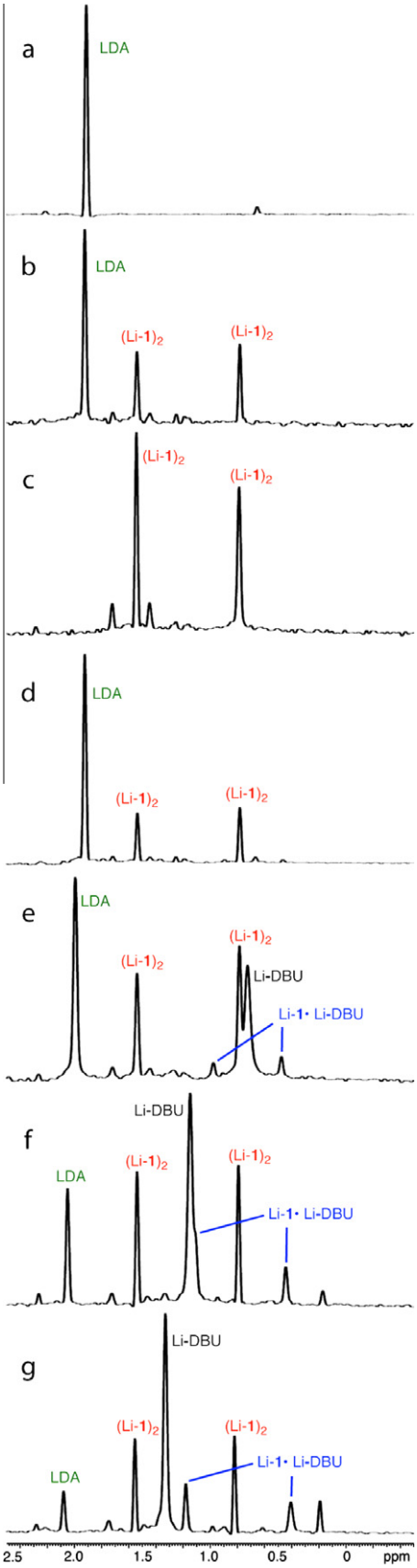


Figure 4. ^{6}Li NMR spectra obtained at −90 °C of a THF-d_8 solution of 0.3 M LDA and added **1**, *n*-Bu[^{6}Li] and DBU: (a) 0.3 M LDA; (b) 0.5 equiv **1**; (c) 1.0 equiv **1**; (d) 1 equiv *n*-Bu[^{6}Li]; (e) 1 equiv DBU; (f) 2 equiv DBU; 3 equiv DBU.

shown in Figure 4e. Apparently, LDA has deprotonated DBU to yield lithiated DBU. In this mixture the molar ratio between LDA and (Li-DBU)$_2$ is about 1:1. The signal from lithiated DBU (∂ 0.72) shifts downfield indicating a solvation by DIPA, which is in accordance with previous observations.[15] The two small peaks at ∂ 0.97 and ∂ 0.47 indicate the presence of the mixed dimer Li-**1**·Li-DBU. Further addition of DBU (1.3 equiv, 0.26 mmol) led to the formation of more lithiated DBU and the accompanying formation of DIPA. This resulted in a shift of the Li-DBU signal to lower field (∂ 1.15). The two mixed dimer signals at ∂ 1.11 and ∂ 0.44 increased in the ^{6}Li spectrum (Fig. 4f). Addition of more DBU (1 equiv, 0.2 mmol) shifts the Li-DBU signal even more downfield (∂ 1.32) (Fig. 3g). The ^{13}C NMR spectrum of the solution shows two signals at ∂ 164.9 and ∂ 165.3 consistent with the presence of lithiated DBU and the mixed dimer Li-**1**·Li-DBU, respectively. Under the catalytic deprotonations, the DBU concentration is typically 5–7 times higher than the LDA concentration, which suggests lithiated DBU is the major bulk base in solution.

2.1.4. The addition of DIPA to (Li-1)$_2$

The addition of diamine **1** (1 equiv, 0.2 mmol) to a solution of *n*-Bu[^{6}Li] (0.2 mmol, 0.3 M) in THF-d_8 at −90 °C yielded a clear, yellow solution. The ^{6}Li spectrum showed the same features as found previously (spectra not shown). The addition of DIPA (0.1 equiv, 0.2 mmol) did not lead to any observable changes in the ^{6}Li spectrum, showing that (Li-**1**)$_2$ is not a strong enough base to deprotonate diisopropylamine.

Addition of *n*-Bu[^{6}Li] (1 equiv, 0.2 mmol) deprotonated the formed diisopropylamine yielding a ^{6}Li spectrum with mainly signals from LDA (∂ 1.60) and (Li-**1**)$_2$ (∂ 1.20 and ∂ 0.40). Addition of another equivalent of DIPA (0.1 equiv, 0.2 mmol) showed no significant changes in the ^{6}Li spectrum. Finally, the ^{6}Li spectra after addition in portions of DBU (0.5 equiv, 1 equiv, 2 equiv, 3 equiv) show the formation of Li-DBU and mixed dimer at the expense of LDA.

2.2. Kinetic study

In order to obtain information about the composition of the rate limiting activated complexes involved in the stoichiometric and the catalytic deprotonation of cyclohexene oxide, the reaction orders of the deprotonation reaction were determined via measurement of the initial rates at different concentrations of each reactants. The deprotonations of **2** yielding **3** were carried out in THF at 0.0 ± 0.1 °C.

The initial rates for the formation of **3** were determined with a quench-extraction-GC procedure and the conversions of the reaction were typically lower by a few percent. The logarithm of the initial rates was plotted against the logarithm of the concentrations of the varying component and the reaction orders were obtained from the gradient. It should be remembered that the reaction orders obtained are related to the change in composition on going from the reactants to the activated complex, and therefore must be related to the composition of the initial state. Knowledge of the major reagent species does not imply that the composition of the activated complex is also known. However, kinetics may yield reaction orders with respect to the reagents, and these inform us about the composition of the activated complexes, as long as the composition of the reagent is known. Several previous studies have shown the complexity of the composition of the activated complexes related to the organolithium compounds in the solution.[24–26]

2.2.1. Catalytic deprotonation of 2 with Li-1, excess Li-DBU and DBU in THF

The initial reaction rates have been determined for the deprotonation of cyclohexene oxide **2** with Li-DBU as a bulk base and free DBU as an additive in THF at 0 °C (Table 1). In these initial rate measurements, the concentrations of Li-**1**, epoxide **2**, DBU and Li-DBU have been varied independently in order to acquire information about how the initial rate is influenced by a change in concentration of each component in the catalytic system. The composition of the standard catalytic deprotonation system is Li-**1** (0.0050 M, 5 mol % of epoxide concentration) and a large excess of Li-DBU (0.20 M, 40 times Li-**1**) and DBU (0.805 M). Under these conditions, the chiral lithium amide is present as a mixed dimer, Li-**1**·Li-DBU, which is the reference state that relates to the reaction orders obtained. The logarithms of the initial rates for formation of **3** were plotted against the logarithms of the concentration for each component of the catalytic system.

$$\text{Li-}\mathbf{1}\cdot\text{Li-DBU} + \mathbf{2} + \text{DBU} \leftrightharpoons [\text{Li-}\mathbf{1}\cdot\mathbf{2}\cdot\text{DBU}]^{\ddagger} + \text{Li-DBU} \rightarrow \mathbf{3} \quad (1)$$

$$K^{\ddagger} = \frac{[\text{Li-}\mathbf{1}\cdot\mathbf{2}\cdot\text{DBU}]^{\ddagger}[\text{Li-DBU}]}{[\text{Li-}\mathbf{1}\cdot\text{Li-DBU}][\mathbf{2}][\text{DBU}]} \quad (2)$$

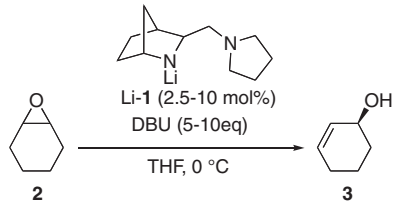
$$[\text{Li-}\mathbf{1}\cdot\mathbf{2}\cdot\text{DBU}]^{\ddagger} = K^{\ddagger}\frac{[\text{Li-}\mathbf{1}\cdot\text{Li-DBU}][\mathbf{2}][\text{DBU}]}{[\text{Li-DBU}]} \quad (3)$$

$$d[\mathbf{3}]/dt = k_{obs}[\text{Li-}\mathbf{1}\cdot\text{Li-DBU}]^{1}[\mathbf{2}]^{1}[\text{DBU}]^{1}[\text{Li-DBU}]^{-1} \quad (4)$$

The reaction orders for the lithium amide Li-**1** and epoxide **2** were determined to 0.94 and 1.04, respectively (Figs. 5 and 6). In addition, the reaction order of free DBU was determined to 0.98 (Fig. 7). This suggests that the composition of the activated complex would be built from a mixed dimer Li-**1**·Li-DBU and one molecule of cyclohexene oxide **2** with one additional molecule of DBU solvating to lithium in the activated complex.

However, upon variation of the concentration of the bulk base Li-DBU, it was found that the initial rate of the reaction increased at lower concentrations (and decreased at higher concentrations) of Li-DBU, relating to a reaction order of −0.97 (Fig. 8). This suggests that the activated complex is not composed of a mixed dimer,

Table 1
Initial rates obtained from runs with different concentrations of Li-**1**, **2**, DBU and Li-DBU in THF at 0.0 °C yielding 2-cyclohexen-1-ol **3**



Li-**1** (M)	**2** (M)	DBU (M)	Li-DBU (M)	Initial rates (10^7 M)
0.0025	0.10	0.805	0.20	13.6
0.0025	0.10	0.805	0.20	12.1
0.0050	0.10	0.805	0.20	23.5
0.0050	0.10	0.805	0.20	23.4
0.0050	0.10	0.805	0.20	24.0
0.0050	0.10	0.805	0.20	23.3
0.010	0.10	0.805	0.20	49.6
0.010	0.10	0.805	0.20	45.7
0.0050	0.050	0.805	0.20	10.5
0.0050	0.050	0.805	0.20	11.7
0.0050	0.20	0.805	0.20	46.0
0.0050	0.10	1.14	0.20	34.0
0.0050	0.10	1.14	0.20	35.1
0.0050	0.10	1.815	0.20	51.1
0.0050	0.10	0.805	0.10	51.5
0.0050	0.10	0.805	0.10	46.0
0.0050	0.10	0.805	0.15	37.7
0.0050	0.10	0.805	0.30	18.2

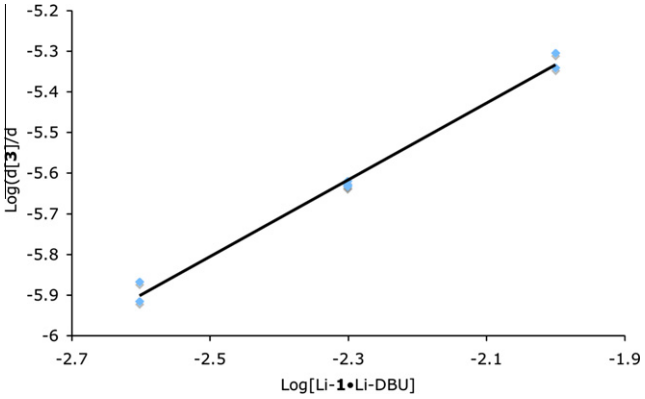


Figure 5. Plot of log[d[**3**]/dt] versus log[Li-**1**] in THF for the catalytic deprotonation of cyclohexene oxide (**2**, 0.10 M) in the presence of Li-DBU (0.20 M) and free DBU (0.805 M) at different concentrations of Li-**1** at 0 °C. The reaction order was obtained as the slope (0.94) of the line.

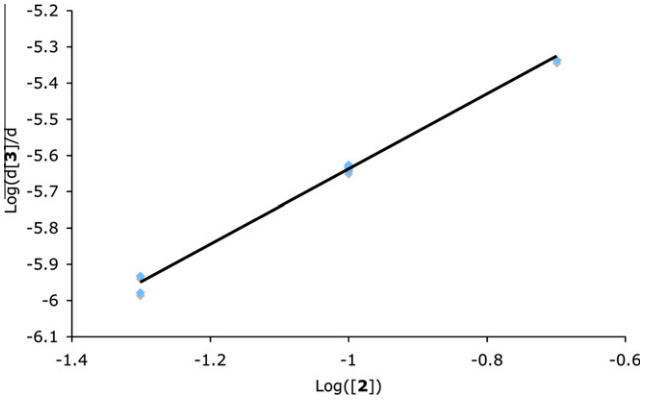


Figure 6. Plot of log[d[**3**]/dt] versus log[**2**] in THF for the catalytic deprotonation of cyclohexene oxide at different concentrations with Li-**1** (0.0050 M) in the presence of Li-DBU (0.20 M) and free DBU (0.805 M) at 0 °C. The reaction order was obtained as the slope (1.04) of the line.

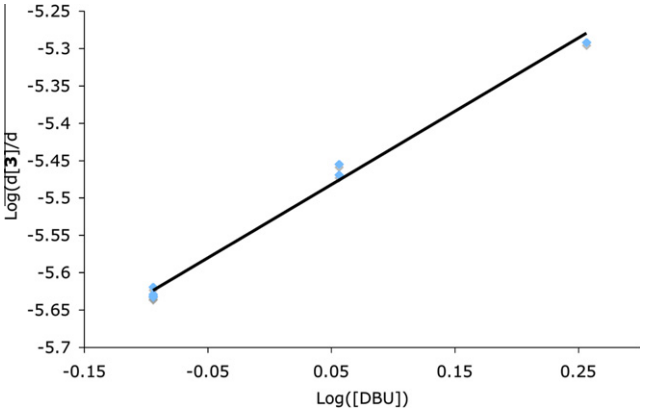


Figure 7. Plot of log[d[**3**]/dt] versus log[DBU] in THF for the catalytic deprotonation of cyclohexene oxide (**2**, 0.10 M) with Li-**1** (0.0050 M) in the presence of Li-DBU (0.20 M) at different concentrations of free DBU at 0 °C. The reaction order was obtained as the slope (0.98) of the line.

but rather of a monomer of the lithium amide Li-**1**, the epoxide **2** and one additional molecule of DBU (Eq. 1–4). The reason for the observed rate acceleration, with DBU as an additive/bulk base, can be explained by DBU coordinating into the monomeric activated complex, which is stabilized compared to the activated

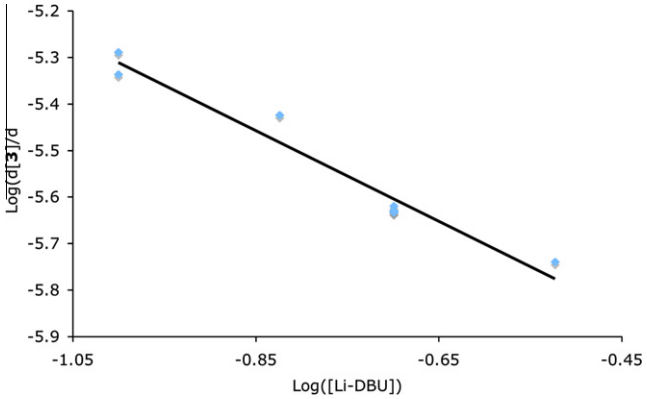


Figure 8. Plot of log[d[**3**]/dt] versus log[Li-DBU] in THF for the catalytic deprotonation of cyclohexene oxide (**2**, 0.10 M) with Li-**1** (0.0050 M) in the presence free DBU (0.805 M) at different concentrations of Li-DBU at 0 °C. The reaction order was obtained as the slope (−0.97) of the line.

complex of the mixed dimer. This is in contrast to DBU which deaggregates the dimer into monomers of the initial state in the solution.

3. Conclusion

The solution structure of Li-**1** in THF was determined to be mainly composed of a dimer (Li-**1**)$_2$ with two non-equivalent lithiums. It has also been shown that the addition of DBU does not cause any major changes to the composition of the lithium amide dimer (Li-**1**)$_2$, that is, the lithium amide does not deaggregate into a monomeric structure or deprotonate DBU to form a mixed dimer.

Bulk bases such as LDA have previously been shown to deprotonate DBU, and thus form lithiated DBU. Li-DBU deprotonates **1** and forms Li-**1**. Li-**1** in the presence of Li-DBU forms a equilibrium of the dimeric lithium amide (see above, (Li-**1**)$_2$) Li-DBU, and the mixed dimer Li-**1**·Li-DBU. Under catalytic conditions, that is, 0.005 M Li-**1** and 0.2 M Li-DBU, the mixed dimer Li-**1**·Li-DBU is the main lithiated species together with Li-DBU. The composition of the activated complex for the catalytic deprotonation of cyclohexene oxide with Li-**1** in THF, excess Li-DBU and free DBU is built from a monomer of Li-**1**, one molecule of cyclohexene oxide, and one additional molecule of DBU. This shows that the mixed dimer deaggregates from Li-**1**·Li-DBU to the monomer Li-**1** solvated by DBU on going to the transition state.

Previous interpretations have suggested that additives of DBU deaggregate the lithium amide dimer into monomers in solution, and this would be the reason for the acceleration of the deprotonation reaction upon addition of DBU. Herein, it has been shown that the chiral lithium amide Li-**1** in the presence of excess Li-DBU forms a mixed dimer Li-**1**·Li-DBU in solution. However, in the activated complex for the deprotonation of **2**, Li-**1**·Li-DBU decomposes to an activated complex composed of Li-**1**·**2**·DBU.

4. Experimental

4.1. General

All of the syringes and NMR tubes used were dried overnight in an oven. All handling of the compounds were carried out with gas-tight syringes. THF-d_8 was stored over molecular sieves (4 Å) in the glove box. DBU was purified by distillation from CaH_2 over nitrogen and diisopropylamine was distilled from NaOH over nitrogen. *n*-Bu[^{6}Li] were prepared as previously described.[27] The chiral diamine **1** was synthesized as previously described and all spectro-

scopic data were in accordance with that previously published.[7,19,28]

4.2. NMR spectroscopy

All NMR experiments were performed in Wilmad tubes (5 mm) fitted with a Wilmad/Omnifit Teflon valve assembly (OFV) and a Teflon/Silicon septum. All NMR spectra were recorded with a Varian Unity 500 spectrometer equipped with a 5-mm triple-resonance probe head, built by Nalorac. Measuring frequencies were 499.9 MHz (^{1}H), 125.7 MHz (^{13}C) and 73.57 MHz (^{6}Li). The ^{1}H and ^{13}C spectra were referenced to signals from residual protons at C2 (δ 1.73) and from C2 carbon (δ 67.57), respectively, in the solvent THF-d_8. Lithium resonances were referenced to external [^{6}Li] in a 0.3 M [^{6}Li]Cl in MeOH-d_4 (δ 0.0) in a separate NMR tube. The probe temperature was measured using a calibrated methanol thermometer from Varian Inc.

4.3. Typical NMR experiment

Diamine **1** (38 μl, 0.2 mmol) was added to an NMR tube containing THF-d_8 (650 μl). [^{6}Li]-**1** was prepared by titration of **1** with *n*-Bu[^{6}Li]. DBU (30 μl, 0.2 mmol, 1 equiv) was added and the solution was allowed to equilibrate for 15 min before spectra were recorded at −90 °C.

4.4. Typical kinetic procedure

Amine (1*R*,3*S*,4*S*)-3-(1-pyrrolidinyl)methyl-2-azabicyclo-[2.2.1]-heptane **1** (2.5 μl, 2.0 M 0.0050 mmol), from a stock solution in THF, was added in a reaction vessel under nitrogen, followed by DBU (150 μl, 1.0 mmol). Next, THF (717 μl) was added, followed by the addition of *n*-butyllithium (80 μl, 0.2 mmol, 2.48 M in hexanes) under a nitrogen atmosphere. The yellow reaction solution was allowed to equilibrate at 0.00 ± 0.05 °C for 15 min in a thermostat. The reaction was started by the addition of cyclohexene oxide **2** (50 μl, 2.0 M in THF, 0.1 mmol) and samples (50 μl) were withdrawn from the reaction vessel at approximately 1–2 min intervals and quenched in hydrochloric acid solution (100 μl, 0.6 M saturated with sodium chloride). Compounds **2** and **3** were extracted with carbon tetrachloride (500 μl) containing the standard 1-hexanol (3.08 mM) and were then placed on ice. The liquid phases were separated by centrifugation and 250 μl of the organic phase was transferred to a vial and analyzed by capillary gas chromatography. Gas chromatography analyses were performed on a Varian 3400 chromatograph equipped with an 8200 Cx auto sampler and a flame ionisation detector (FID). For the separation an achiral DBWX-30W column (30 m, 0.25 μm) from Varian Inc. was used with hydrogen as the carrier gas (2 ml min^{-1}). Reaction samples (1.0 μl) were introduced onto the column via a split injector (split flow 15 ml min^{-1}) and the components were separated using a temperature programme. Initially the temperature was held at 80 °C for 2 min and then during 2 min it was increased to 120 °C. The injector temperature was 225 °C and the detector was held at 250 °C. Gas chromatography response factors for **2** and **3** were determined, using 1-hexanol as a reference, to 1.01 and 0.85, respectively.

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